

Please replace the paragraph beginning at page 7, line 1, with the following rewritten paragraph:

Preferably, the polymorphism of the carbamyl phosphate synthetase polypeptide comprises an A to C transversion in exon 36 of the CPSI gene, more preferably at nucleotide 4340 of a cDNA that corresponds to the CPSI gene. More preferably, the A to C transversion at nucleotide 4340 of the cDNA that corresponds to the CPSI gene further comprises a change in the triplet code from AAC to ACC, which encodes a CPSI polypeptide having a threonine moiety at amino acid 1405.

Please replace the paragraph beginning at page 19, line 11, with the following rewritten paragraph:

The primers of the invention embrace oligonucleotides of sufficient length and appropriate sequence so as to provide initiation of polymerization on a significant number of nucleic acids in the polymorphic locus. The CPSI locus is depicted schematically in Fig. 5. Specifically, the term "primer" as used herein refers to a sequence comprising two or more deoxyribonucleotides or ribonucleotides, preferably more than three, and more preferably more than eight and most preferably at least about 20 nucleotides of the CPSI gene wherein the DNA sequence contains the A to C transversion at base 4340 relative to CPSI contained in SEQ ID NO's:1 and 3. The allele including cytosine (C) at base 4340 relative to CPSI is referred to herein as the "CPSIa allele", the "T1405 allele", or the "threonine-encoding allele". The allele including adenosine (A) at base 4340 relative to CPSI is referred to herein as the "CPSIb allele", the "N1405 allele", or the "asparagine-encoding allele".

Please replace the paragraph beginning at page 56, line 17, with the following rewritten paragraph:

Where a CPSI gene itself is employed it will be most convenient to simply use a wild type CPSI gene directly. The CPSI gene can thus comprise the threonine encoding allele such that amino acid 1405 of the encoded polypeptide comprises threonine. Alternatively, the CPSI gene comprises the asparagine encoding allele such that amino acid 1405 of the encoded polypeptide comprises asparagine.

Additionally, it is envisioned that certain regions of a CPSI gene can be employed exclusively without employing an entire wild type CPSI gene or an entire allelic variant thereof. It is proposed that it will ultimately be preferable to employ the smallest region needed to modulate the urea cycle so that one is not introducing unnecessary DNA into cells which receive a CPSI gene construct. Techniques well known to those of skill in the art, such as the use of restriction enzymes, will allow for the generation of small regions of an exemplary CPSI gene. The ability of these regions to modulate the urea cycle can easily be determined by the assays reported in the Examples. In general, techniques for assessing the modulation of the urea cycle are known in the art.

Please replace the paragraph beginning at page 61, line 23, with the following rewritten paragraph:

Optionally, the supplementation therapy method of the present invention further comprises the step of initially detecting a polymorphism of a carbamyl phosphate synthase I (CPSI) gene in the subject. The polymorphism of the carbamyl phosphate synthetase polypeptide preferably comprises an A to C transversion within CPSI exon 36, more preferably comprises an A to C transversion at nucleotide 4340 of a cDNA that corresponds to the CPSI gene, and even more preferably, the A to C transversion at nucleotide 4340 of the cDNA that corresponds to the CPSI gene further comprises a change in the triplet code from AAC to ACC, which encodes a CPSI polypeptide having a threonine moiety at amino acid 1405.

Please replace the paragraph beginning at page 83, line 16, with the following rewritten paragraph:

Genotyping. DNA was isolated using a QIAmp™ blood kit (Qiagen). The T1405N polymorphism changes the DNA sequence as follows:

CCT-GCC-ACC-CCA-GTG (SEQ ID NO:21)	Normal
CCT-GCC-AAC-CCA-GTG (SEQ ID NO:22)	Change

Please replace the paragraph beginning at page 84, line 21, with the following rewritten paragraph:

In accordance with the present invention, a common polymorphism near the 3' end of the CPSI mRNA (about .44 heterozygosity) has been identified. Sequence analysis of this change revealed a C to A transversion at base 4340 changing the triplet code from ACC to AAC. This results in a substitution of asparagine for threonine at amino acid 1405 (referred to herein as "T1405N"). The threonine is within the allosteric domain, preceding the signature sequence PV(A/S)WP(T/S)(A/Q)E (SEQ ID NO:23), a sequence that is important in the binding of the cofactor n-acetyl-glutamate (NAG).

Please replace the paragraph beginning at page 98, line 9, with the following rewritten paragraph:

Since there is no gender disparity in the occurrence of HVOD, we concentrated on potential pharmacogenetic issues related to CPSI, an autosomally encoded gene, rather than on the X-linked ornithine transcarbamylase gene. While characterizing the molecular changes underlying the causes of neonatal and late-onset CPSI deficiency, a common SNP near the 3' end of the CPSI mRNA (0.44 heterozygosity) was identified. This C4340A transversion encodes a predicted substitution of asparagine (AAC) for threonine (ACC) at amino acid 1405 (T1405N). This threonine is within the allosteric domain, preceding the sequence PV(A/S)WP(T/S)(A/Q)E (SEQ ID NO:23) important in the binding of a cofactor, n-acetyl-glutamate (NAG), that increases enzyme activity. Although applicants do not wish to be bound by any particular theory of operation, it is speculated that based on the precedent of the effects of other xenobiotics, that limited availability of NAG after escalated dose chemotherapy is one of the mechanisms promoting urea cycle dysfunction. Nonetheless, it appears that the presence of the CPS-I SNP AA genotype is associated with protection against the development of HVOD, resolution of ALI if it occurs, and improved 60 day survival after BMT. Thus, the data suggest that alteration in UC function plays a role in modifying liver-lung interaction during sepsis and acute lung injury.